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(54) Title: TAZAROTENE AND CORTICOSTEROID TREATMENT FOR PSORIASIS

(57) Abstract

The present invention provides a method for treating proliferative skin diseases comprising the administration of an effective amount of tazarotene and an effective amount of a corticosteroid. This invention is especially useful for treating psoriasis.

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TAZAROTENE AND CORTICOSTEROID TREATMENT FOR PSORIASIS

CROSS REFERENCE TO RELATED APPLICATIONS

This patent application claims priority from Provisional Patent Application 60/03915 filed on February 20, 1997.

BACKGROUND OF THE INVENTION

1. FIELD OF THE INVENTION

This invention relates to pharmaceutical compositions for application to the skin and to a method for the treatment of proliferating skin diseases. The composition may be applied topically. The treatment can be either therapeutic or prophylactic.

2. DESCRIPTION OF RELATED ART

Proliferative skin diseases are widespread throughout the world and afflict millions of humans and their domesticated animals. This invention provides a method for treatment of such diseases. As used hereinafter in this specification and in the claims, the expression "proliferative skin diseases" means benign and malignant proliferative skin diseases which are characterized by accelerated cell division in the epidermis, dermis or appendages thereto, associated with incomplete tissue differentiation. Such diseases include: psoriasis, atopic dermatitis, non-specific dermatitis, primary irritant contact dermatitis, allergic contact dermatitis, basal and squamous cell carcinomas of the skin, lamellar ichthyosis, epidermolytic hyperkeratosis, premalignant sun-induced keratosis, non-malignant

keratosis, acne, and seborrhic dermatitis in humans and atopic dermatitis in domesticated animals.

Heretofore, proliferative skin diseases have been generally accepted by mankind as an ongoing evil having degrees of severity variable with inherited skin traits and external factors but always have been recognized as unsightly, painful, morbid diseases. Over the history of mankind innumerable medicines and treatments have been proposed, tried and used with varying degrees of success.

Treatments which are prescribed and used for the treatment of proliferative skin diseases include the following:

(1) topical applications, e.g. coal tar derivatives, 5-fluorouracil, vitamin A acid, glucocorticoids in high dosage, bath oils and non-specific emollient creams and ointments;

(2) systemic administration, e.g. glucocorticoids and classic anti-cancer agents, for example, methothrexate, hydroxyurea, azaribine, cyclophosphamide; and

(3) physical modalities, e.g. ultra violet light, x-radiation, and, in severe cases, surgery.

While these treatments provide, in certain cases some remission of the original symptoms, each treatment suffers some defect, for example, temporary and incomplete mitigation of symptoms, rapid re-occurrence of the disease when mitigation is terminated, serious and sometimes irreversible damage (atrophy) resulting from the topical application for extended times of glucocorticoids, acute bone marrow suppression, cirrhosis of the liver resulting from the protracted use of methothrexate which may lead to death of the patient, and the causation of cancer by the application of anti-cancer drugs, x-radiation, or ultra violet rays.

Recently, a new compound has been approved by the Food and Drug Administration for the treatment of psoriasis and acne. Tazarotene. Tazarotene is available as Tazorac® 0.1% and Tazorac® 0.05% topical gel from Allergan, Inc. of Irvine, California.

BRIEF SUMMARY OF THE INVENTION

The present invention relates to a method of treating psoriasis in humans with tazarotene, preferably a gel comprising 0.1%, tazarotene by weight, and a corticosteroid, preferably a cream. The tazarotene gel may be administered once daily in the evening and the corticosteroid cream may be administered to the subject once daily in the morning, or the gel and cream may be administered on alternate days. The tazarotene gel is disclosed in U.S. patent Application Serial no. 623,184, which is entitled "Stable Gel Formulation for Topical Treatment of Skin Conditions", which was filed on March 28, 1996, in the name of Prakash Charu and is hereby incorporated by reference in its entirety.

In one aspect of the invention, the corticosteroid may be Synalar® cream (0.01% fluocinolone acetonide), Elocon® cream (0.1% mometasone furoate) or Lidex® cream (0.05% fluocinonide), i.e. a low-potency, mid-potency and high-potency corticosteroid, respectively.

In another aspect of the invention, the corticosteroid may be fluocinonide 0.05% ointment, Lidex®, a high potency steroid, mometasone fuoate 0.1% ointment, Elocon®, a high potency steroid, diflorasone diacetate 0.05% ointment, Maxiflor®, a high potency steroid, fluticasone propionate 0.005% ointment, Cultivate®, a mid-potency steroid, betamethasone dipropionate 0.05% cream, Diprosone®, a mid-potency steroid, diflorasone diacetate 0.05% cream, Maxiflor®, a mid-

potency steroid, clobetasol propionate 0.05% ointment, Temovate®, a super-potency steroid, betamethasone valerate 0.1% lotion, Valisone®, a mid-potency steroid.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph comparing the reduction in plaque elevation over a 12 week treatment period with tazarotene in combination with placebo, high-potency corticosteroid, mid-potency corticosteroid and low-potency corticosteroid.

Figure 2 shows the treatment success with the combination therapies of Figure 1.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with this invention it has been found that proliferative skin diseases are alleviated, that is, the symptoms of the disease are noticeably improved or become undetectable, by the treatment of the afflicted patient, or animal, with the pharmaceutical compounds described in detail, hereinbelow.

For the purposes of this specification and the claims, a proliferative skin disease is alleviated when there is a noticeable decrease in the thickness of a lesion to palpation, with or without residual redness, or residual slightly dilated blood vessels or residual hyper- or hypo-pigmentation. For purposes of this invention and the claims hereof, psoriasis is alleviated when a scale-free psoriasis lesion is noticeably decreased in thickness, or noticeably but incompletely cleared or completely cleared.

The compositions utilized in the method of this invention may be applied topically.

The term "topical" as employed herein relates to the use of the active ingredient incorporated in a suitable pharmaceutical carrier, and applied at the site of the disease for exertion of local action. Accordingly, such topical compositions include those pharmaceutical forms in which the compound is applied externally by direct contact with the skin surface to be treated. Conventional pharmaceutical forms for this purpose include ointments, lotions, pastes, jellies, sprays, aerosols, bath oils and the like. The term "ointment" embraces formulations (including creams) having oleaginous, absorption, water-soluble and emulsion-type bases, e.g., petroleum, lanolin, polyethylene glycols, as well as mixtures thereof. Topical application with occlusion of an area larger than the medicated area may produce improved results relative to non-occluded topical applications.

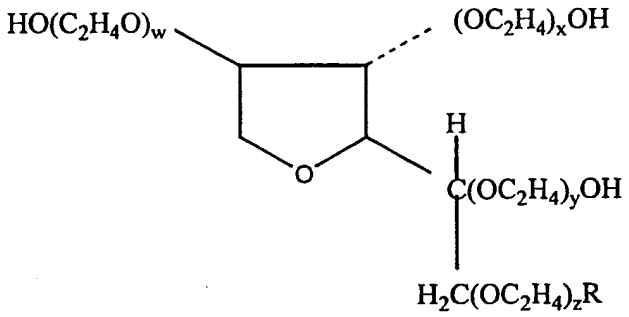
The percentage by w/w of the active ingredient, i.e. the corticosteroid herein utilized ranges from about 0.001% to about 1% of the pharmaceutical preparation, preferably from about 0.005% to about 0.1%, by weight.

The percentage by w/w of the active ingredient, i.e. tazarotene herein utilized ranges from about 0.01% to about 15% of the pharmaceutical preparation, preferably from about 0.1% to about 2% and in these preparations the aforesaid pharmaceutical carrier for topical application constitutes a major amount of the said preparation.

Preferably tazarotene is utilized as a stable gel formulation for topical treatment of skin conditions in humans, said stable gel formulation comprising: Ethyl-6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate in a plurality of nonaqueous vehicles for both solubilizing tazarotene and forming a gel therewith, said nonaqueous vehicles enabling topical application of the gel to a skin condition, said plurality of vehicles each

being present in amounts, and in combination, to control release of tazarotene from the gel to the skin conditions. In the tazarotene formulation the vehicles are present in amounts selected to produce maximum release of the active agent, i.e. tazarotene, from the gel when all the vehicles are present therein. Preferably the formulation comprises three vehicles and more preferably the formulation comprises three vehicles which are used to both solubilize the active agent and form a gel.

The formulation preferably comprises the three vehicles, e.g. Polysorbate 40, Poloxamer 407 and Hexylene glycol. Polysorbate 40 is



wherein the Sum of w, x, y, and z is 20 and R is $(C_{15}H_{31})COO$ and Poloxamer 407 is $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$ having the following properties.

USAN for Poloxamers

Poloxamer	Physical Form	Average Molecular Weight	Average Values a	Average Values b	BASF Corp. Brand Name
124	Liquid	2090 to 2360	12	20	L 44
188	Solid	7680 to 9510	80	27	F 68
237	Solid	6840 to 8830	64	37	F 87
338	Solid	12700 to 17400	141	44	F 108
407	Solid	9840 to 14600	101	56	F 127

More preferably, tazarotene is utilized as a stable gel formulation for topical treatment of psoriasis comprising an effective amount of Ethyl-6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate in a pharmaceutical carrier comprising:

(a) water;
(b) edetate disodium;
(c) ascorbic acid;
(d) Carbomer 934P;
(e) Poloxamer 407;
(f) polyethylene glycol;
(g) Polysorbate 40;
(h) hexylene glycol;
(i) butylated hydroxytoluene;
(j) butylated hydroxyanisole;

(k) benzyl alcohol; and

(l) tromethamine.

The tazarotene formulation may comprise Polysorbate 40 in an amount up to about 0.4% by weight, Poloxamer 407 in an amount up to about 0.4% by weight, and hexylene glycol in an amount up to about 2% by weight or more preferably Polysorbate 40, in an amount of about 0.32% by weight, Poloxamer 407 in an amount of about 0.18% by weight, and hexylene glycol in an amount of about 2% by weight.

Most preferably, the tazarotene formulation comprises:

INGREDIENT	FUNCTION	CONCENTRATION %W/W
tazarotene	Drug	0.1
purified water	Excipient	49.25
Edetate Disodium	Stabilizer	0.05
Ascorbic acid	Stabilizer	0.05
Carbomer 934P[1]	Thickening agent	1.25
Poloxamer 407	Surfactant	0.2
PEG-400	Co-solvent	45.0
Polysorbate 40	Surfactant	0.2
Hexylene glycol	Co-solvent	2.0
Butylated hydroxytoluene	Stabilizer	0.05
Butylated hydroxyanisole	Stabilizer	0.05
Benzyl alcohol	Preservative	1.0
Triethanolamine/ Tromethamine	Neutralizer	0.8

[1]Carbomer 934P [1975]. NF. The viscosity of a neutralized 0.5 percent aqueous dispersion of Carbomer 934P is between 29,400 and 39,400 centiposes. (1) Polymer of 2-propenoic acid, cross-linked with allyl ethers of sucrose or pentaerythritol; (2) Polymer of acrylic acid, cross-linked with allyl ethers of sucrose or pentaerythritol. Molecular weight is approximately 3,000,000.

The tazarotene formulation and the corticosteroid formulation, each, will be applied, topically, in an amount to achieve the maximum effect on alleviating the proliferative skin disease symptoms without causing an adverse reaction. Selection of such an amount of either formulation is well within the skill of the art.

Preferably, the tazarotene formulation is utilized to provide from about 0.5 to about 5 mg of tazarotene per cm^2 of affected skin, more preferably from about 1 to about 3 mg/cm^2, e.g. 2 mg/cm^2.

The method of this invention also employs a corticosteroid. The expression "corticosteroid" refers to a naturally occurring product of the adrenal cortex, or a synthetic analog thereof possessing anti-inflammatory activity and minimal or no mineralocorticoid activity or sex steroid activity. The corticosteroids include glucocorticoids. Of the natural glucocorticoids, one may use for example, hydrocortisone or the synthetic glucocorticoids such as methyl prednisolone acetate (Prednisone) or triamcinolone for topical therapy. The corticosteroids are preferably employed in amounts of from 0.5 to 5 mg per cm^2 of affected skin, more preferably from about 1 to 3 mg/cm^2, e.g. 2 mg/cm^2.

The treatment period may be 12 weeks with a 4 week follow-up period. The subjects are evaluated for plaque elevation, scaling and erythema with a successful treatment defined as about 50% improvement or better. During the treatment period, tazarotene in combination with the mid- or high-potency corticosteroid produced significantly better results than treatment with tazarotene in combination with placebo in reducing plaque elevation, scaling, erythema and overall severity. During the 4 week post-treatment period, the results with tazarotene plus mid- or high-potency corticosteroid were equal to or better than tazarotene plus placebo or tazarotene plus low-potency corticosteroid.

The most common adverse events resulting from the treatment were burning, pruritus and erythema; however there was a lower incidence of such adverse events in patients treated with tazarotene plus the medium- or high-potency corticosteroid.

Thus, treating psoriasis in humans with a combination of tazarotene and a mid-potency or high-potency corticosteroid is more effective than a combination of tazarotene and low-potency or placebo and results in a lower incidence of adverse events such as burning pruritis and erythema.

The invention is further illustrated by the following examples which are illustrative of various aspects of the invention, and are not intended as limiting the scope of the invention as defined by the appended claims.

EXAMPLE 1

The study reported here utilizes a combination regimen that alternates between tazarotene 0.1% gel and a corticosteroid or placebo cream every evening. The aim of the study was to determine whether such alternating therapy may offer clinical benefits by maximizing the therapeutic benefits of both drugs, while also minimizing corticosteroid use and thus reducing the potential for adverse corticosteroid-induced effects.

This study was a multicenter, investigator-masked, parallel-group study, enrolling 398 patients with stable plaque psoriasis. Topical applications of tazarotene 0.1% gel, were administered every other evening, and one of the following creams administered on alternate evenings): placebo; low-potency corticosteroid (hydrocortisone acetate 1%); medium-potency corticosteroid (alclometasone dipropionate 0.05%); or high-potency corticosteroid (betamethasone valerate 0.1%).

The study required a 12-week treatment period plus a 4-week follow-up phase. The patient demographics included 388 patients (231 male and 157 female) with evaluable data, mean age of 46.7 years (range: 21-88 years) and a mean duration of psoriasis of 17.39 years.

All treatment groups achieved clinically significant reductions in plaque elevation at all treatment and post-treatment visits, with the tazarotene/high-potency combination taz/high group achieving consistently greater reductions than

the other treatments throughout the study. At week 4, these reductions were significantly greater than those in all the other treatment groups. The taz/high also achieved clinically significant reductions in plaque elevation more rapidly than the other treatments, i.e. in two weeks compared with four weeks in all the other groups. (See the results set forth in Figure 1.)

Treatment success was defined as a moderate, marked, almost clear or completely cleared response ($\geq$ 50% global clinical improvement). All tazarotene/corticosteroid treatment groups achieved treatment success rates of > 50% within 4 weeks. However, the taz/high combination achieved significantly greater treatment success rates than the tazarotene/placebo (taz/plac) and tazarotene/medium-potency corticosteroid (taz/med) combinations throughout the 12-week treatment period. Peak treatment success rates ranged from 56% (for patients treated with taz/plac at Week 8) to 77% (for taz/high at Week 8).

During the 4-week follow-up period, all groups retained $\geq$60% global clinical improvements in psoriasis, with treatment success rates ranging from 60% (for taz/med) to 75% (for taz/high) at study Week 16. These improvements were statistically and clinically significant compared with the pretreatment levels and there were no significant differences between the groups at the end of the follow-up period. (See Figure 2.)

Week 12, the probability of patients being considered a treatment success at any study visit was 77% in the taz/high group. In the other groups the treatment success was 56 to 61%.

The taz/high combination also achieved initial treatment success significantly faster than any of the other combinations. The median time to treatment success was 2 weeks in the taz/high group, compared with 4 weeks in each of the other groups.

All treatment groups achieved clinically significant reductions in scaling during the treatment period, and the taz/high combination was consistently the most efficacious treatment throughout the 12-week treatment period. The reductions in

scaling achieved in all groups by the end of the treatment period were generally maintained during the 4-week follow up period.

All treatment groups achieved statistically significant reductions in erythema during the treatment period and, once again, the taz/high combination was the most efficacious treatment. During the follow-up period, all groups retained significant reductions in erythema compared with baseline levels, and these reductions were clinically significant in the taz/high, taz/med, and taz/plac groups.

The overall incidence of adverse events that were possibly, probably or definitely treatment-related decreased with increased corticosteroid potency, falling from 42% in the taz/plac group, to 36%, 32% and 31% in the tazarotene/low-potency corticosteroid (taz/low), taz/med, and taz/high groups, respectively. (See Table II, below.)

Table II. Overall incidence of adverse events

	Patients (%)			
	Taz/plac	Taz/low	Taz/med	Taz/high
Pruritus	15	19	16	8
Erythema	12	7	6	6
Irritation	8	9	5	4
Burning	6	4	4	8

In view of the above Example, the following conclusions may be drawn. Alternate-day treatment with tazarotene 0.1% gel and the high potency corticosteroid cream was consistently more effective than the other three regimens in reducing plaque elevation, scaling and erythema. Patients in the tazarotene plus high-potency corticosteroid group also achieved significantly higher treatment

success rates (≥ 50% global clinical improvement, and achieved treatment success faster, than patients in the other groups. Treatment-related adverse events comprised mainly mild to moderate local irritation including pruritus, erythema and burning skin. The incidence of treatment-related adverse events decreased as the potency of the corticosteroid cream used increased.

EXAMPLE 2

The study of Example 1 is substantially repeated with fluocinolone acetonide 0.01% cream (low-potency), mometasone furoate 0.1% cream (mid-potency) and fluocinonide 0.05% cream (high-potency) used as the corticosteroids. In this study tazarotene 0.1% gel in combination with a mid-potency or high-potency corticosteroid, when compared with tazarotene plus placebo cream, was associated with significantly higher treatment success rates, significantly greater reductions in scaling, erythema, and overall lesional severity, with a decreased incidence of adverse events. The corticosteroids are Synalar® cream, Elocon® cream and Lidex® cream, respectively.

While particular embodiments of the invention have been described, it will be understood of course that the invention is not limited thereto since many obvious modifications can be made and it is intended to include within this invention any such modifications as will fall within the scope of the appended claims.

Having now described the invention, I claim.

1. A method for treating proliferative skin diseases comprising the administration of an effective amount of tazarotene and an effective amount of a corticosteroid.

2. The method of claim 1 wherein said corticosteroid is selected from the group consisting of fluocinolone acetonide, mometasone furoate, fluocinonide, diflorasone diacetate, fluticasone propionate, betamethasone dipropionate, clobetasol propionate, betamethasone valerate.

3. The method of claim 1 wherein tazarotene is applied as a 0.1% gel.

4. The method of claim 1 wherein said corticosteroid is a mid- or high-potency corticosteroid.

5. The method of claim 4 wherein said corticosteroid is selected from the group consisting of mometasone furoate and fluocinolone acetonide.

6. A method for treating psoriasis in a human subject by topically applying to the psoriatic skin of said subject an effective amount of tazarotene and an effective amount of a corticosteroid.

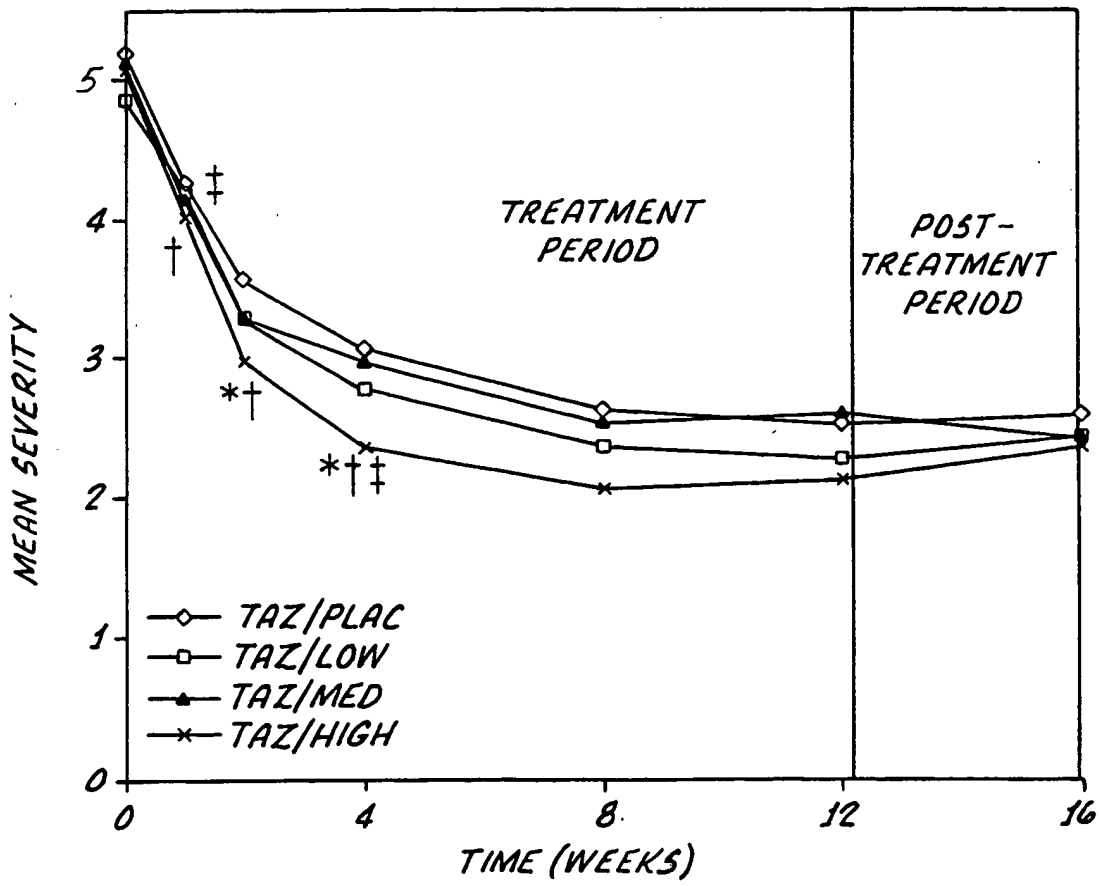
7. The method of claim 6 wherein tazarotene is applied as a 0.1% gel.

8. The method of claim 7 wherein said corticosteriod is a cream.

9. The method of claim 8 wherein said corticosteroid is a mid- or high-potency corticosteroid.

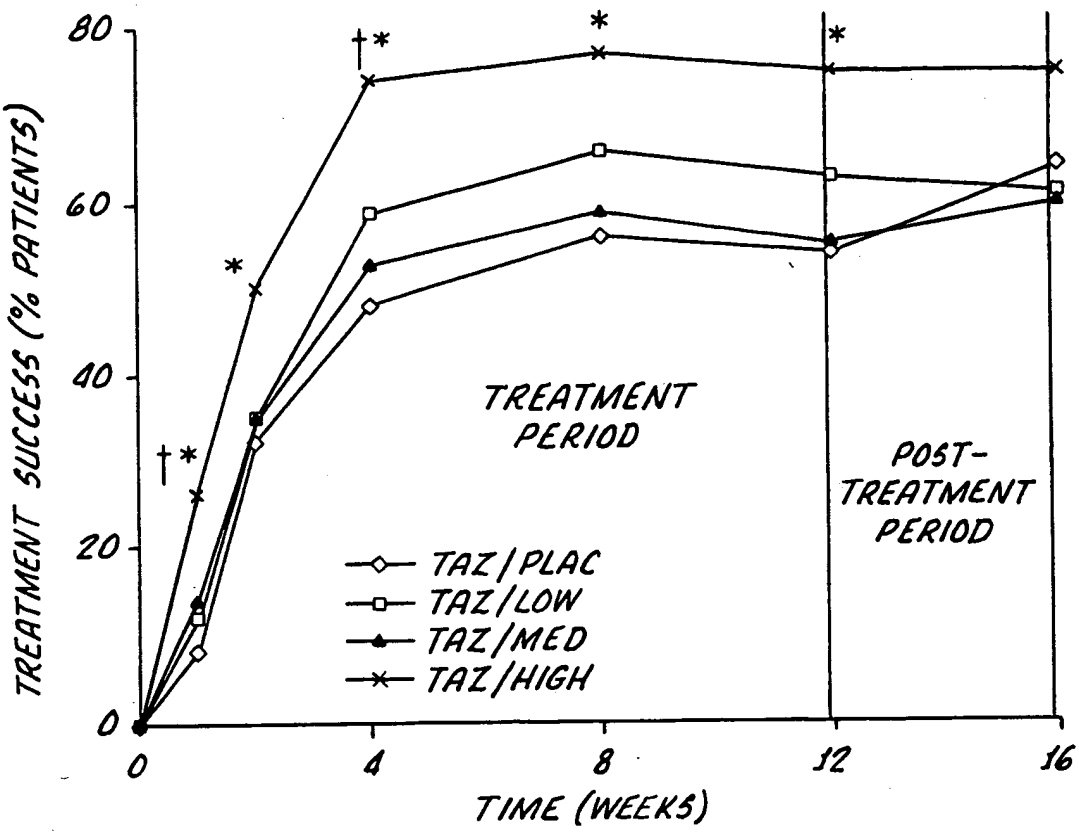
10. The method of claim 9 wherein said corticosteroid is selected from the group consisting of mometasone furoate and fluocinolone.

11. The method of claim 6 wherein tazarotene is administered once daily in the evening and the corticosteroid is administered once daily in the morning.



*P < 0.05 VS TAZ/PLAC;
†P < 0.05 VS TAZ/LOW;
‡P < 0.05 VS TAZ/MED.

FIG. 1.



*P < 0.05 VS TAZ/PLAC AND TAZ/MED
†P < 0.05 VS TAZ/LOW

FIG. 2.

INTERNATIONAL SEARCH REPORT

Intern ..onal Application No
PCT/US 98/03355

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/57 //(A61K31/57,31:44)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BIOLOGICAL ABSTRACTS, vol. 10, Philadelphia, PA, US; abstract no. 981998, SCHWARTZ E ET AL: "In vivo prevention of corticosteroid-induced skin atrophy by tretinoin in the hairless mouse is accompanied by modulation of collagen, glycosaminoglycans, and fibronectin" XP002067726 see abstract & JOURNAL OF INVESTIGATIVE DERMATOLOGY, 102 (2). 1994. 241-246., --- -/--	1-11

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 June 1998	01. 07. 1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Leherte, C

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inten. ...nal Application No
PCT/US 98/03355

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BIOLOGICAL ABSTRACTS, vol. 31, Philadelphia, PA, US; abstract no. 16902, VAN DER RHEE H J ET AL: "COMBINED TREATMENT OF PSORIASIS WITH A NEW AROMATIC RETINOID TIGASON IN LOW DOSAGE ORALLY AND TRIAMCINOLONE ACETONIDE CREAM TOPICALLY A DOUBLE-BLIND TRIAL" XP002067727 see abstract & BR J DERMATOL, 102 (2). 1980. 203-212.,	1-11

1

INTERNATIONAL SEARCH REPORT

Int. ational application No.
PCT/US 98/03355

Box I Observations where certain claims were found unsearchable (Continuation of item 1 f first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.